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BACTERIEMIA DUE TO BACILLUS DIPHThERIAE *

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Clinical diphtheria is a thoroughly studied disease which is characterized by the localization of *B. diphtheriae* on certain of the mucous membranes, usually of the larynx, pharynx, or nasal cavities, from which original foci the infecting agent may spread by continuity or by transplantation. The toxins, evolved by the metabolic activities of the bacteria in the affected tissues, are rapidly absorbed, and it is the presence of these bodies circulating in the blood stream which rapidly gives rise to systemic symptoms.

Certain variation in the site of infection and in pathogenicity of the invading organism should be borne in mind. Not infrequently, cases of what has been termed "concealed diphtheria" occur, in which infection has been established for some time in inaccessible regions, usually the nasal cavity, before extending sufficiently to be recognized.

REVIEW OF LITERATURE

Terrien¹ has reviewed this condition at some length and cites numerous cases in which the throat was not invaded at any time. Altho it is not uncommon for the deeper air passages and the lungs themselves to become involved by the extension of a diphtheric process, these tissues are but very infrequently the primary site of the infection. More or less numerous cases of diphtheric infection of various other tissues occur, either primarily or as a result of transplantation. The list of these is extensive, including the eye, ear, esophagus, stomach, bladder, vagina, rectum, and various parts of the skin surface, and even a meningeal complication has recently been reported. As for the toxicity of various strains of the diphtheria bacillus, there have been reported very wide differences, and some strains, otherwise typical, produce no diphtheria toxin.

While the infection itself is usually purely focal the organisms may enter the blood stream in greater or lesser numbers. The frequency of this invasion and the time and extent of its occurrence are difficult questions. The post mortem bacteriological examination of the blood and viscera has yielded some information. Loeffler is said to have found the organism in the inner organs, and several workers have published the results of studies of such material. These findings seem to be exemplified fairly well by those

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1. *Ann. de méd. et chir. inf.*, 1911, 15, p. 5.
2. *Jour. Boston Soc. Med. Sc.*, 1898, 2, p. 92.

of Pearce.² He made cultures from the heart's blood, spleen, liver, and kidney of a large series of fatal cases of uncomplicated diphtheria and of diphtheria complicated with scarlet fever, measles, and bronchopneumonia, and found the diphtheria bacillus in one or more of these sites in a fairly large proportion of cases, either alone or in conjunction with streptococci. The latter type of organism was found alone in a larger percentage than the diphtheria bacillus alone, particularly in the complicated cases. Particularly pertinent to the present discussion is the fact that the diphtheria bacillus was isolated from the heart's blood much less frequently than from the solid organs. In this series, it was recovered from the blood in but six of one hundred and forty cases, or 4.3 percent. In three instances, it was mixed with streptococci, in the others it was recovered in pure culture. In Banhoff's³ series of three hundred and fourteen fatal cases it was recovered from the heart's blood in thirteen instances (4.1 percent), in only three of which cases was it unmixed. In none of these reports is the concentration of the organisms indicated, nor is there any possibility of ascertaining over what period of time the organisms had been present, that is, whether the hematic dispersion was not terminal. Pearce remarks that positive results of tissue cultures occurred most frequently, tho not always, in the gravest cases, known as "septic" diphtheria.

Under the name "diphtheria septicque," certain authors designate a very severe, overwhelming type of diphtheric infection, a vivid description of which is given by Baginsky,⁴ who speaks of it as "septicemic general diphtheria." This is not synonymous with diphtheric septicemia (or bacteriemia) for the former appellation depends solely on the clinical manifestations and in no way refers to actual determination of "septic," or other invasion of the blood stream by micro-organisms.

Definite diphtheria bacteriemia characterized by the persistence and multiplication of organisms in the blood stream is evidently very infrequent, and there are but few reported instances in which there is even a strong probability of its occurrence. Hiss and Zinsser⁵ even go so far as to assert that while the organisms may be found in the organs post mortem we have no data which would justify the assumption that a true diphtheria septicemia may occur during life.

Howard⁶ described very carefully an interesting instance of ulcerative endocarditis due to the diphtheria bacillus, in which the point of entry was not determined. Cultures from various organs and sections of tissues, removed eight hours post mortem, showed more or less numerous organisms identified as diphtheria bacilli. The incidence and number of these were held to indicate a bacteriemic invasion secondary to the endocarditis.

3. Ztschr. f. Hyg. u. Infektionskrankh., 1910, 67, p. 349.

4. Quoted by Jacobi: Diseases of Children, 1910, p. 739.

5. Textbook of Bacteriology, 1910, p. 511.

6. Am. Jour. Med. Sc., 1894, 108, p. 651.

Neissen,⁷ having recovered the Klebs-Loeffler bacillus in pure culture from the blood of a 9-year-old boy, published apparently the first case of ante mortem blood stream isolation. This organism was not subjected to pathogenicity tests. Roosen-Runge's⁸ case was probably one of a true septicemia, since the first culture was confirmed by a second positive blood culture and by the post mortem discovery of an ulcerative endocarditis in which the diphtheria organisms were demonstrated. Mahler⁹ secured the organism in two out of three blood cultures in his case, indicating either a considerable scarcity of organisms or an inconstancy of the blood invasion. Ucke's¹⁰ report was based on the discovery of a single colony of an organism morphologically the diphtheria bacillus on one of several tubes inoculated with the patient's blood by a confrère and brought to him for examination. A second blood culture was negative. Diphtheria-like organisms were seen among many staphylococci and streptococci in the pus from a gluteal abscess, but these were not differentiated from skin-inhabiting, diphtheria-like saprophytes. In view of these facts and of the proven absence of toxicity in the organism primarily isolated, the possibility of mistaking a non-pathogenic "diphtheroid" for the diphtheria bacillus must, in this case, be particularly considered. Hesse¹¹ obtained a positive blood culture in a case which developed an infective endocarditis due to the same organism. Leede¹² obtained both the streptococcus and an organism identified as the diphtheria bacillus from the circulating blood of a case in which the bacillary invasion did not persist and only the coccus could be obtained from the heart's blood at autopsy. Morgan,¹³ who has most recently reviewed the literature, records a case in which he isolated an organism corresponding to the diphtheria bacillus from the venous blood thirty-six hours ante mortem.

It is particularly interesting that in the seven cases reported as instances of ante mortem blood invasion of the diphtheria bacillus, the organisms isolated were said to be either entirely non-pathogenic, or of extremely low virulence in the four cases in which animal tests were performed. These cases were those of Roosen-Runge, Mahler, Ucke, and Morgan. Howard's organism, recovered post mortem, was also non-pathogenic.

In recent years, several attempts have been made by cultural work with urine from patients in various stages and with various types of diphtheria and from convalescents, to determine whether or not this disease is essentially a bacteriemia. Nicoll and Wilcox¹⁴ investigated this question in 1913, and reviewed the previous work done. This may be summarized as follows: Conradi and Bierast examined the urine of one hundred and fifty-five patients with fifty-four positive results. None of these cases was followed to study the persistence. But six virulence tests were made, all with positive results. R. Koch examined one hundred and eleven urines from twenty-six patients. In four specimens from two patients, virulent diphtheria organisms were obtained, and in ten specimens from five other patients, diphtheria-like organisms which were either not obtained in pure culture or which were non-virulent were also obtained. Beyer reported results which were almost incredible, since in nineteen cases the specimens examined daily or every other day gave posi-

7. Wien. med. Wchnschr., 1902, 47, p. 2221

8. München. med. Wchnschr., 1903, 39, p. 1252.

9. Berl. klin. Wchnschr., 1917, 47, p. 1499.

10. Centralbl. f. Bakteriöl., Orig., 1908, 46, p. 292.

11. Deutsch. med. Wchnschr., 1909, 35, p. 1096.

12. Ztschr. f. Hyg. u. Infektionskrankh., 1911, 70, p. 104.

13. Am. Jour. Dis. Child., 1913, 5, p. 317.

14. Ibid., 6, p. 23, Am. Jour. Obst., 1913, 68, p. 167.

tive results in practically all examinations. It may here be added that Freifeld,¹⁵ stimulated by his interest in a case of persistent pseudomembranous infection of the mucous membrane of the bladder caused by a non-toxin-producing strain of the diphtheria bacillus, culturally examined the urine in ten other cases of diphtheria. From four of these he recovered the organism.

Since the results of the earlier workers had proven inconclusive, Nicoll and Wilcox¹⁴ undertook to satisfy themselves as to the appearance of the diphtheria organism in the urine during the course of the disease. Using rather more favorable media than those previously employed, they studied fifty-six specimens from fifty-four patients in varying stages and with various degrees of infection. But two positive cultures were obtained, and these specimens were negative on second examination some days later. They concluded that their two positive findings may have been due to contamination, and that, tho the organisms may very occasionally gain access to the blood and be excreted by the urine, this fact is of theoretic interest only.

Authentic cases of diphtheria-septicemia are undoubtedly very rare, and it has been thought worth while to describe a case of bronchopneumonia which came under the observation of the writer. On account of the presence of bubonic plague in this city during the summer of 1914 and because of the fear that an obscure case of this infection might pass unrecognized, particularly careful admission examinations were made of all patients who presented themselves with a hyperpyrexia not clearly explainable. In many of these cases in which suspiciously enlarged lymph nodes were present, material for examination was obtained by aspiration of the nodes. Frequently a blood culture was also made. As a consequence of this scrutiny, there was seen in consultation with the Admitting Officer of the Charity Hospital a case suffering from fever and prostration, in which was detected a focus of bronchopneumonia and a bilateral tonsillitis of slight extent. Two throat cultures made at the time of admission later proved negative of the diphtheria bacillus, while a blood culture taken at the same time, twenty-two hours before death, showed virulent diphtheria bacilli estimated by count to have been present in a concentration of about 1,600 viable organisms per cubic centimeter of blood.

HISTORY OF CASE

A. H., a colored boy 7 years of age, was brought to the hospital by his parents July 8, 1914, complaining of fever, pain in the left side of the chest, sore throat, and a considerable degree of prostration. The boy told of having had this sore throat for over a week but, according to his mother, he was rather suddenly taken ill three or four days previously, with moderate fever and a cough, the nature of which is not known.

15. Berl. klin. Wchnschr., 1913, 1, p. 1761.

Examination showed the patient to be rather poorly developed and nourished. A general lymphadenopathy was discovered, the glands being symmetrically enlarged, firm, discrete, and not tender. The femoral, inguinal, axillary, cervical, and epitrochlear nodes were easily palpated, but the femoral and inguinal groups seemed especially enlarged. The heart was increased in size and the pulsations were plainly to be seen over the entire left side. The apex beat was in the mid-axillary line. On auscultation a systolic murmur was noted, clearest at the apex. A small area of dulness was made out in the left axilla, over which mucous râles were heard. Throat examination revealed a small, whitish patch on each tonsil, not typical of diphtheria, and not seriously thought to be such. Voice was slightly hoarse but there was no evidence of respiratory obstruction. Respirations were 60 per minute, the temperature 103.5 F., and the pulse 136, full and bounding.

Altho the case was thought not to be bubonic plague, in view of the sudden onset and the degree of prostration out of proportion to the meager physical findings, the possibility of this infection had to be considered. As a part of the strict precautionary measures in vogue at the time, one of the enlarged femoral nodes was aspirated and smears and cultures made from the few drops of material thus obtained. In order to isolate possibly a virulent pneumococcus from the blood stream, a blood culture was also made. The blood was withdrawn by a sterile all-glass syringe with a capacity of 2 c.c. from a vein in the arm after thorough application of iodine to the skin. Three tubes of warm, melted, sterile agar were inoculated and poured into sterile plates. A flask of sterile broth was also inoculated. Two throat cultures were made on Loeffler's serum slants, one from each tonsil. As the smears from the gland fluid showed nothing suggestive of the bacillus pestis, the patient was sent to a ward, in the service of Dr. J. B. Guthrie.

During the night his respirations were jerky and very rapid. At times he moaned and cried in sleep, and changed his position frequently. His temperature continued to rise, until at 4 a. m., it registered 104.6 F. At this time, altho he was very thirsty, he showed difficulty in swallowing and his voice became husky.

The next morning the areas of lung dulness were greater in size and more easily perceived. He now complained of a considerable pain in right elbow. Both throat cultures examined at this time showed only staphylococci and a few streptococci. The cultures from gland fluid showed no evidence of growth of the bacillus pestis. He continued to do badly, moaning and grunting continuously and frequently complained of thirst and drank freely. At noon he became very restless with weak pulse and rapid, jerky, and grunting respirations. At 12:55 he died, twenty-two hours after the cultures were taken. No post mortem examination.

BACTERIOLOGICAL EXAMINATION

The blood agar plates made on admission were examined on the second day after the boy's death. All showed numerous small colonies, both in the depth and on the surface of the medium. Transplants were made and on the following day, because of the suggestive morphology, a full-grown rabbit was injected subcutaneously with a small, washed-down agar culture. Within thirty-six hours the animal died. Examination post mortem showed an edematous inflammatory lesion at the point of inoculation from which the

diphtheria bacillus was grown in pure culture. Other organs showed nothing but congestion. Cultures from the heart's blood, liver, and spleen were negative.

At the time of inoculation of the rabbit, transplants were made into various media, including several tubes of the sugar litmus serum waters of Hiss. At the end of forty-eight hours, these showed acid production with coagulation in dextrose and maltose, and without coagulation in dextrin and levulose. In lactose and galactose there was only slight acid production in seventy-two hours, and in saccharose, mannite and inulin there was no change. This corresponds very closely to the table of reactions given for the diphtheria bacillus by Hiss and Zinsser. Other cultures and the morphology of young organisms grown on Loeffler's blood serum media were all typical of this organism. The morphology on the various media differed widely.

As the final step in the identification of the organism, the influence of specific antitoxic serum on guinea-pigs inoculated with the culture was tested.

On July 19 three pigs were inoculated with a forty-eight-hour broth growth as follows:

Guinea-pig 1.—Given 1 c.c. subcutaneously. The animal was found dead twenty-four hours later. Diphtheria bacilli were recovered from the local subcutaneous lesion only, and cultures from the spleen and liver showed no growth.

Guinea-pig 2.—Given 1,000 units of diphtheria antitoxin intraperitoneally, and five minutes later 1 c.c. of the broth culture given Guinea-pig 1 was administered subcutaneously. This pig is alive one month later.

Guinea-pig 3.—Given 2 c.c. of the toxic culture subcutaneously, and fifteen minutes later 2,000 units of antitoxin intraperitoneally. The animal was very ill for two or three days, after which it recovered completely.

Many writers emphasize the fact that streptococci or staphylococci are also found in a large proportion of cases in which the diphtheria bacillus is found post mortem in the heart's blood or viscera. These accompanying bacteria are assigned an important rôle in the invasion of the blood stream by the diphtheria organism. It was thought desirable to determine whether or not either of these organisms was present in this case, and with this point in mind, two of the plates were studied in detail on the seventh day of their incubation. With the exception of a few large colonies of frank surface contaminators on one plate, all of the surface colonies were rather dense, opaque, and yellowish white. Each colony showed a central heaping up, and about this elevation was coarsely granular and irregularly punctate.

The deep colonies were rather small, lenticulate to round in shape, and were reddish or brownish in color, probably from absorption of blood pigment. They were firm, and often came out of the agar on the wire as a small, solid, yellowish mass. No other type of colony was present.

Sixty transplants were made from two plates. Twenty of these were from surface colonies; three of them being from evident contaminators transplanted to ascertain the type. Forty of these inoculations were made from a single area on one of the plates, and every visible colony in that area was transplanted. On the following day, smears from fifty-seven of the transplants showed the usual intensely gram-positive bacilli, many of which showed distinct polar bodies. The three contaminators, which were transplanted, were found to belong to the *B. proteus* and *B. subtilis* groups. Fifty more smears were then made directly from other colonies on the original plates; on examination all showed diphtheria morphology.

A striking feature of the plates studied was the large number of diphtheria colonies present. Since the amount of blood used in making the plates was known to be 0.2-0.3 c.c. per plate, it was a simple matter to estimate the number of organisms per cubic centimeter of blood. On one plate there were counted 400 and on the second 418 colonies. If we take the amount of blood used as 0.25 c.c. there were roughly 1,600 organisms viable in vitro per cubic centimeter of circulating blood.

In speculating on this heavy invasion of the blood stream so long before death, it was thought that possibly the organism was of low virulence and had been multiplying in the blood stream for a comparatively long period of time, while producing but moderate symptoms. Altho it was evident from the symptoms and post mortem cultures that the experimental animals died from toxic and not "septic" effects of the organisms injected, no real indication had been obtained of the actual amount of toxin produced by the organism. Experiments were therefore carried out to determine the degree of toxin production in vitro.

A thin layer of neutral broth in a large flask was inoculated with the organism and incubated for nine days. This culture was drawn through a Berkefeld filter and diluted, and guinea-pigs were inoculated. Each guinea-pig was given a total volume of 4 c.c. of dilutions of various strengths, under the skin of the abdomen.

Guinea-pig 1 (275 gm.) received 0.04 c.c. of the original toxic broth, and thirty-six hours after the inoculation the animal was found dead; Guinea-pig 2 (268 gm.) received 0.02 c.c. of original toxin, and sixty hours after the inoculation the animal was found dead; Guinea-pig 3 (261 gm.) received

0.01 c.c. of toxin, symptoms for several days, recovered and was alive and well one month after inoculation; Guinea-pig 4 (252 gm) received 0.005 c.c. of toxin, symptoms slight. Alive and well.

It is therefore to be concluded that the minimum lethal dose of toxic broth produced by this strain of diphtheria bacillus is between 0.02 c.c. and 0.01 c.c. or, roughly, 0.015 c.c. for guinea-pigs of about 250 gm. One cubic centimeter would therefore contain 66.66 M. L. D. for guinea-pigs of this weight, which is a fairly high potency for such broth cultures.

DISCUSSION

While it is not a rare development in diphtheria that the surface infection and pseudomembrane should extend along the air passages or should by inhalation be transplanted to deeper levels, it is rare for the primary infection to be of the pulmonary tissues. Indeed, few authors recognize the possibility of this occurrence. That the present case is of this type can only be suggested in view of the rather meager clinical observations and the absence of autopsy. In favor of the pulmonary origin of the infection the principal evidence is negative. There was no complaint of any affection of the nasal chambers, nor was there any sign of coryza or of embarrassed nasal respiration noted. Altho there was a moderate inflammatory condition of the tonsils, no characteristic pseudomembrane was present, and two cultures made from the pharynx on standard serum showed only staphylococci with a few streptococci. The presence of tonsillitis, even of a non-diphtheric nature, might argue the primary lesion to be here, but it seems improbable that the organisms should have completely disappeared when once established. That the negative report on the throat cultures was erroneous can scarcely be maintained. These facts, together with evident lung involvement, led to the clinical diagnosis of bronchopneumonia, altho the physical findings did not indicate an extensive lesion.

The source of the organisms found in the blood culture can scarcely be questioned. The colonies were discrete and well separated and were uniformly distributed through and on the surface of the medium in the three blood agar plates, in only one of which was surface air contamination found. The technic employed at the bedside was as elaborate as is usually used in blood culture work. Therefore, there is no possibility that the organisms found could have come from the skin or other source of contamination.

The nature of the organism has been thoroughly established. The identification work was carried out with particular care on account of our realization of the danger of confusing organisms of the "diphtheroid" group. Morphologically and tinctorially identifiable as the diphtheria bacillus and similarly fatal to laboratory animals, the culture reacts as this organism in sugar serum waters and in proper broth cultures produces a strong toxin which is neutralized by diphtheria antitoxin. This specific protection by diphtheria antitoxin of animals injected with toxin is held by some to be of considerable importance in the identification of the diphtheria bacillus. Nevertheless, Park and Williams,¹⁶ who emphasize this point, also discuss organisms, like the one from Morgan's case, which are morphologically and culturally similar to the diphtheria bacillus, but which are not toxin producers. They consider these as strain variants, possibly through attenuation.

In no case of so-called diphtheria bacteriemia in the literature was the organism proven typically pathogenic or to produce specific diphtheria toxin, a fact which makes the present case more unusual.

The condition of extensive bacteriemia and concurrent toxemia in the case described was it is believed responsible for the death of the patient, while the pulmonary lesions were yet of but moderate extent. That the bacteriemia was a secondary manifestation of the infection is undoubted, but that it cannot be considered terminal or agonal, comparable to the majority of Pearce's cases, for instance, is maintained on account of the length of time before death at which the culture was taken and the great number of organisms present in the blood at that time. Furthermore, the condition of the patient when admitted, while serious, did not suggest the rapid termination that ensued.

The frequency of a temporary blood invasion, or metastasis, in diphtheria is apparently not very low. In cases of least severity, or in those in which controlling doses of antitoxin are given early, the localized nature of the infection is probably maintained throughout. When, however, treatment is begun very late in the infection, when the patient's resistance is low, in cases of greatest severity and particularly those in which the organisms tend to multiply rapidly rather than to produce especially potent toxin, and finally in those in which local secondary invasion of the streptococcus, staphylococcus,

16. *Pathogenic Bacteria and Protozoa*, 1910, p. 205.

or pneumococcus aids in the dissemination of the organisms, there is a greater probability of encountering a systemic infection. In such cases, the presence of a greater or less number of the bacteria in the organs may be expected as a result of accidental transportation and prompt removal of bacteria from the blood stream by these organs.

In a condition such as that in the case described, in which there was no medication and in which the lesion was apparently pulmonary, the general invasion is not surprising. Here the vascularity and permeability of the affected tissue would play a considerable part in the inauguration of the blood infection on account of more or less constant invasion of the capillaries of the congested lung tissue by the bacteria. Possibly, as Howard suggested in his case, the constant addition of many bacteria to the blood caused the ultimate exhaustion of the inhibiting influences, with subsequent multiplication of the organisms in the circulation.

The superiority of the *intra vitam* blood culture over other methods of studying the bacteriemia of diphtheria is here exemplified. Post mortem studies, however carefully carried out, are inconclusive. Not only are the cases studied of the less common, fatal type, but, in case of positive cultures from the blood, the length of time of the blood infection and the concentration of the organism is entirely unsettled. Other factors vitiating the results of this study are terminal dissemination and post mortem invasion and multiplication. Such findings, therefore, indicate the frequency of ultimate invasion of the blood and deeper tissues in fatal cases, but have little bearing on the ante mortem condition of the average case of diphtheria during the course of the disease. The frequency of negative results, particularly of the heart's blood cultures, in the fatal cases seems much more significant indicating the relative infrequency of general blood infection.

As may be expected when so many determining factors, such as technic, cases and their environment, stages of disease and standards of identification are concerned, the results of urine examinations vary widely in the hands of different observers. These range from the more credible negative findings of Nicoll and Wilcox to the nearly all positive results of Beyer. The apparent value of any of these results seems greatly diminished when one considers that the irregular and inconstant percolation of bacteria through the kidneys and their detection in the urine is depended on to indicate the frequency of diphtheria bacteriemia. It is here necessary but to call attention to the urine culture findings in typhoid fever, a disease essentially a bac-

teremia early in its course, and in which as high as 95 percent of positive blood cultures have been reported. According to different authorities, the typhoid bacilli are not apt to be found in the urine until the second or third week of the fever, and after that they may be found in 17-25 percent of cases. This comparison also appealed to Freifeld,¹⁵ who furthermore called attention to the work of Stufina and Dietman,¹⁷ who cultivated the vibrio of Asiatic cholera from the urine in 5-6 percent of a series of cholera. It would seem evident, therefore, that no accurate deduction can be drawn as to the occurrence of bacteremia in an infection from a study of the bacteriology of the urine.

CONCLUSIONS

It is evident from the number of hours *ante mortem* at which the blood culture was taken and from the great numbers of the bacteria present, that the case presented is one of true bacteremia due to *B. diphtheriae*. From the clinical findings it is concluded that the bacteremia was secondary to a diphtheritic bronchopneumonia, which was probably primary. The organism isolated is a strain of the diphtheria bacillus of fairly high toxicity and is the only typically toxic strain known to have been isolated from a similar condition.

In the consideration of diphtheria bacteremia there should be drawn a sharp distinction between the condition of metastasis, or accidental blood infection or contamination, which might occur in any severe local infection and which apparently not infrequently does occur in diphtheria, and the condition of true bacteremia, which is of much more serious import and which in diphtheria is apparently extremely rare.

In the determination of the incidence of systemic infection by diphtheria bacillus, the blood culture is the logical procedure since by it alone can one secure direct evidence as to its frequency of occurrence in all types of cases, the numbers of viable organisms present, and, in fatal cases, the length of time before death that the blood dispersion was present.

Urine examinations alone cannot be expected to give any reliable indication of the occurrence of a bacteremia in diphtheria, not only on account of technical difficulties, but because of the great uncertainty of the appearance of the bacteria in the urine, as indicated by the study of this excretion in typhoid fever, a condition known to be bacteremic in nature.

17. Quoted by Freifeld: *Berl. klin. Wchnschr.*, 1913, 1, p. 1761.